Trastuzumab deruxtecan in previously treated HER2-positive metastatic breast cancer: Plain language summary of the DESTINY-Breast01 study

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Summary

This is a summary of the article discussing the results of the DESTINY-Breast01 study originally published in the New England Journal of Medicine. The DESTINY-Breast01 study is a clinical study in participants with a type of breast cancer called HER2-positive breast cancer. The participants in the study received a treatment called trastuzumab deruxtecan, also known as T-DXd. The purpose of this summary is to help you understand the results of the DESTINY-Breast01 study. T-DXd is currently available as a treatment for adults with HER2-positive breast cancer that cannot be removed by surgery, also called unresectable, or that has spread, also called metastatic. In the DESTINY-Breast01 study, all the participants had HER2-positive breast cancer that was metastatic or unresectable. All participants were required to have had previous treatment for their HER2-positive breast cancer with another treatment, called trastuzumab emtansine or T-DM1. All the participants received T-DXd every 3 weeks. Part 1 was done to learn how T-DXd acted in the body, and to choose a dose to give to all the participants in Part 2. In Part 2, 184 participants received T-DXd at 5.4 mg/kg and the results showed that T-DXd reduced tumor growth. Up to 60.9% of the participants had their tumors shrink or disappear, with a treatment response that lasted for nearly 15 months on average. The participants lived with their cancer for around 16 months before it got worse. During the study, 183 out of 184 participants had side effects, known as adverse events. The most common adverse event was nausea. There were 42 participants (22.8%) who had serious adverse events, including lung toxicity. These results suggest that T-DXd could be a treatment option for people with metastatic HER2-positive breast cancer who have already been treated with T-DM1. Additional studies will provide more information and results about T-DXd.

How to say (double click to play sound)...

• Trastuzumab: tras-tuh-ZUH-mab
• Deruxtecan: der-UHX-teh-can

Who should read this article?

This summary may be helpful for patients with HER2-positive breast cancer and their family members or caregivers. It may also be helpful for patient advocates and healthcare professionals. This includes those who are looking for treatment options for patients with HER2-positive metastatic breast cancer.

What is HER2-positive breast cancer?

Proteins called human epidermal growth factor receptor 2, also called HER2, are found on the surface of breast cells and help control each cell’s normal growth. In people with HER2-positive breast cancer, too many HER2 proteins cause breast cells to grow and multiply in an uncontrolled way, forming tumors. About 15% to 20% of breast cancers are HER2-positive breast cancers.

Scientists determine if someone has HER2-positive breast cancer by looking at their breast cancer cells collected during a biopsy. Scientists do certain tests on the cells to look at the HER2 proteins under a microscope. This way, the scientists can count the HER2 proteins to see if there are too many.
HER2-positive breast cancers can grow quickly compared to other breast cancers. They are also more likely to either come back after treatment or become metastatic. Metastatic means that the cancer has grown beyond the organ where it started and has spread to other parts of the body.

The participants in the DESTINY-Breast01 study had HER2-positive breast cancer that was metastatic or unresectable.

**What is HER2-positive breast cancer?**

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**What is trastuzumab deruxtecan?**

In this summary, trastuzumab deruxtecan will be referred to as T-DXd. T-DXd consists of a chemotherapy drug linked to a manmade antibody. Chemotherapy drugs work by attacking cancer cells before they can divide and grow. Normally, antibodies are made by the immune system to fight off infections. But, researchers can also make antibodies in a laboratory and use them to treat certain conditions or diseases. The antibody in T-DXd is a protein that specifically targets and attaches to the HER2 protein on tumor cells.

When the antibody attaches to the HER2 protein, T-DXd is taken up into the tumor cell. Once inside, the chemotherapy part of T-DXd is released and the chemotherapy kills the tumor cell. Some of the chemotherapy can spread into nearby tumor cells to kill these too, even if they do not have many HER2 proteins on the surface.

T-DXd works in a similar way to another treatment for HER2-positive breast cancer called trastuzumab emtansine, also called T-DM1. But, T-DXd uses a different chemotherapy drug. Each T-DXd drug has on average 8 of the chemotherapy particles per antibody, while T-DM1 has on average 3–4 chemotherapy particles per antibody.
Why was the clinical study needed?

Treatments for metastatic HER2-positive breast cancer are designed to control the growth of tumors. This can help improve patients’ quality of life and help them live longer.

There are standard treatments that doctors usually use first for patients with HER2-positive breast cancer. These treatments are known as first-line therapies. First-line therapies can stop working over time, so doctors give patients other treatments to help control tumor growth. These are known as second-line or third-line therapies, and so on. In general, many tumors are affected less by second-line and third-line therapies compared with first-line therapies.

In patients with cancer, researchers measure the amount of time between the start of treatment and the cancer spreading or tumors growing. This is known as progression-free survival. This may only be 3 to 6 months after starting third-line therapy.

So, more treatment options are needed for people with metastatic HER2-positive breast cancer that can help control the growth or spread of their tumors, and to lengthen the time before their cancer gets worse or returns.

What was the purpose of the clinical study?

The main questions the researchers wanted to answer in the DESTINY-Breast01 study were:

- Did the participants’ tumors shrink or disappear after receiving T-DXd?
- For how long did the participants’ tumors shrink or disappear before growing again?
- For how long did the participants live with their cancer before it got worse?
- What were the most common adverse events during treatment with T-DXd? An adverse event is any sign or symptom that participants have during a study.

For a full list of the questions that the researchers in this clinical study wanted to answer, please refer to the websites listed at the end of this summary.

Who took part in the clinical study?

The DESTINY-Breast01 study included 253 women aged 18 and older.

All of the participants:

- Had HER2-positive breast cancer that was metastatic or unresectable
- Had previous treatment with TDM-1
- Were able to move around easily or were fully active

People were not able to join the study if they had:

- Metastatic cancer in the brain that had been untreated or was causing symptoms
- Interstitial lung disease, also called ILD, which refers to a number of different non-infectious lung diseases that can cause scarring and stiffness of the lungs
- Pneumonitis, which is inflammation of the lung tissue
What happened during the clinical study?

The study had two parts. Both parts were open label. This means the participants, researchers, study doctors, and other study staff knew what each participant was receiving.

All of the study participants received T-DXd every 3 weeks through a needle put into the veins, also known as an IV infusion. The dose each participant received was based on their body weight. The doses were measured in milligrams per kilogram of body weight, also called mg/kg.

Part 1 was done to find out how T-DXd acted in the body, and to choose a dose to give to all of the participants in Part 2. To do this, the doctors gave different doses to the participants in Part 1 and took blood samples at different times during the study. In Part 1, the researchers used a computer program to randomly choose which dose of T-DXd each participant received. This helped make sure the doses were chosen fairly and comparing the results of the doses was as accurate as possible.

The chart below shows how the study was done:

**Part 1**

- **Part 1a**: finding out how T-DXd doses behave in the body
  - 22 participants got 5.4 mg/kg of T-DXd
  - 22 participants got 6.4 mg/kg of T-DXd
  - 21 participants got 7.4 mg/kg of T-DXd

- **Part 1b**: finding out how well two chosen T-DXd doses work
  - 28 participants got 5.4 mg/kg of T-DXd
  - 26 participants got 6.4 mg/kg of T-DXd

**Part 2**

Finding out how well T-DXd works at the chosen dose of 5.4 mg/kg

- 184 participants got T-DXd at the chosen dose of 5.4 mg/kg
  - 50 participants who had already got 5.4 mg/kg of T-DXd in Part 1a or Part 1b
  - 4 participants who had stopped taking TDM-1 for reasons other than their cancer worsening
  - 130 participants who had already tried TDM-1 but their tumors were still growing
What were the overall results of the clinical study?

Below is a summary of the main results of this clinical study. A full report of the study results can be found on the websites listed at end of this summary. This summary and the full report do not have each participant’s individual results.

Researchers look at the results of many clinical studies to decide which treatments work best and are safest. Additional studies will provide more information and results about trastuzumab deruxtecan.

The results below include information for the 184 participants in Part 2, who received T-DXd at the chosen dose of 5.4 mg/kg.

Did the participants’ tumors shrink or disappear after receiving T-DXd?

To answer this question, the researchers measured the overall response of the participants. This was the main question that the researchers wanted to answer. To calculate the overall response, the researchers counted how many participants:

- had their tumors shrink by more than 30.0%, called a partial response
- had their tumors disappear completely, called a complete response

The researchers measured the participants’ tumors using a computerized tomography scan, also called a CT scan. Then, they analyzed the scans using a set of rules or criteria called Response Evaluation Criteria in Solid Tumors, also called RECIST. These rules define what it means for a tumor to decrease in size (respond), stay the same (stabilize), or increase in size or spread (progress) during treatment.

Based on the results, the researchers calculated the response rate for the participants. To do this, they used a type of average called a median. In a set of numbers, the median is the middle number between the lowest and highest numbers. The researchers found that:

- After receiving T-DXd, the median response rate was 60.9%. This means that 112 out of 184 participants had a treatment response, based on the RECIST criteria.

Some other questions the researchers wanted to answer were about the overall responses in different subgroups of participants. They found similar results in these subgroups, including in participants with tumors that had spread to the brain. These participants had been treated for their tumors in the brain before coming onto the study and the tumors in their brain were stable and not growing.

For how long did the participants’ tumors shrink or disappear before growing again?

To answer this question, the researchers calculated the median number of months that the participants had no tumor growth after their tumors had shrunk or disappeared. This is called the response duration. This was calculated for all of the participants who had a response to treatment during the study.

- The researchers found that the participants’ median response duration was 14.8 months.

For how long did the participants live with their cancer before it got worse?

The researchers calculated the median number of months after starting the study that the participants lived with their cancer before it got worse. This is called progression-free survival. This was calculated for all of the participants who took part in the study.

- The researchers found that the participants’ median progression-free survival was 16.4 months.
What were the most common adverse events during treatment with T-DXd?

The doctors kept track of the adverse events that the participants had during the clinical study. An adverse event is any sign or symptom that participants have during a study. An adverse event is considered serious when it is life-threatening, causes lasting problems, or the participant needs hospital care.

Adverse events may or may not be caused by the treatments in the study. A lot of research is needed to know whether a treatment causes an adverse event.

The results below include information for the 184 participants in Part 2 who had received T-DXd at the chosen dose of 5.4 mg/kg.

**How many participants had adverse events?**

- 99.5% (183 out of 184 participants)

**How many participants had serious adverse events?**

- 22.8% (42 out of 184 participants)

**How many participants died because of adverse events?**

- 4.9% (9 out of 184 participants)

**How many participants stopped getting study treatment because of adverse events?**

- 15.2% (28 out of 184 participants)

Details on the adverse events that led to death include a case each of general deterioration in physical health (0.5%), pneumonia (0.5%), organ failure (0.5%), shut down of the body due to loss of blood (0.5%). There were two cases of interstitial lung disease (1.1%), which were considered to be related to the study treatment.
What were the most common adverse events?
The most common adverse event during the clinical study was nausea.

The results below show the adverse events that happened in at least 14.0% of participants during Part 2. There were other adverse events, but these happened in fewer participants. Some participants may have had more than one adverse event.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Percentage</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>77.7%</td>
<td>(143 out of 184 participants)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>49.5%</td>
<td>(91 out of 184 participants)</td>
</tr>
<tr>
<td>Hair loss</td>
<td>48.4%</td>
<td>(89 out of 184 participants)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>45.7%</td>
<td>(84 out of 184 participants)</td>
</tr>
<tr>
<td>Constipation</td>
<td>35.9%</td>
<td>(66 out of 184 participants)</td>
</tr>
<tr>
<td>Reduction in number of total white blood cells</td>
<td>31.0%</td>
<td>(57 out of 184 participants)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>31.0%</td>
<td>(57 out of 184 participants)</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>29.9%</td>
<td>(55 out of 184 participants)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>29.3%</td>
<td>(54 out of 184 participants)</td>
</tr>
<tr>
<td>Reduction in platelets, part of the blood that helps form blood clots</td>
<td>21.2%</td>
<td>(39 out of 184 participants)</td>
</tr>
<tr>
<td>Reduction in neutrophils, a type of white blood cell</td>
<td>21.2%</td>
<td>(39 out of 184 participants)</td>
</tr>
<tr>
<td>Headache</td>
<td>19.6%</td>
<td>(36 out of 184 participants)</td>
</tr>
<tr>
<td>Cough</td>
<td>19.0%</td>
<td>(35 out of 184 participants)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>16.8%</td>
<td>(31 out of 184 participants)</td>
</tr>
<tr>
<td>Reduction in lymphocytes, a type of white blood cell</td>
<td>14.1%</td>
<td>(26 out of 184 participants)</td>
</tr>
</tbody>
</table>
What were the most common adverse events? (continued)

In other clinical studies with T-DXd, the participants had certain adverse events. The researchers wanted to learn if the participants in this study also had these same adverse events. These are called adverse events of special interest.

One of these adverse events of special interest is interstitial lung disease, also called ILD. This term refers to different non-infectious lung diseases that cause scarring of the lungs, also called fibrosis. This scarring causes stiffness in the lungs which makes it difficult to breathe and to get oxygen to the bloodstream. ILD can also include pneumonitis, which is when the lungs become inflamed.

During the study, any participants with signs and symptoms of ILD were required to stop receiving T-DXd right away and be treated with steroids.

The signs and symptoms of ILD include fever, cough, or shortness of breath. Patients and their doctors should carefully monitor for these signs and symptoms so that ILD can be found early and treated.

The researchers found that during Part 2 of the study:

- ILD happened in 13.6% of participants. This was 25 out of 184 participants.
- Most ILD cases (20 out of 184) were mild or moderate in severity.
- There were 4 participants who died because of ILD.
- At the end of the study, 19 of the participants had recovered or were receiving treatment.

What do the results of this clinical study mean?

The results from this study showed that overall, T-DXd reduced tumor growth in participants who had already received treatment with TDM-1 for their metastatic or unresectable HER2-positive breast cancer.

The result showed that up to 60.9% of the participants had their tumors shrink or disappear, with a response duration of nearly 15 months. The participants lived with their cancer for around 16 months before it got worse.

The results also showed that people receiving T-DXd may have an increased risk for ILD. Patients and their doctors should carefully monitor for the signs and symptoms of ILD and be open to discussing these, so it can be found early and treated.

The results from this clinical study suggest that T-DXd could be a treatment option for people with metastatic or unresectable HER2-positive breast cancer who have already been treated with T-DM1. Patients should always talk to a doctor before making any decisions about their treatment.

Who sponsored the clinical study?

Daiichi Sankyo Co., Ltd., and AstraZeneca funded this study. The study was designed and led by Daiichi Sankyo Co., Ltd., for data collection and analysis, and was approved by the institutional review board at each participating site. In March 2019, AstraZeneca entered into a collaboration agreement with Daiichi Sankyo Co., Ltd., for trastuzumab deruxtecan. Both Daiichi Sankyo Co., Ltd., and AstraZeneca were involved in study oversight and data collection. All authors and sponsors assisted in data interpretation, writing the report, and reviewing the manuscript. All authors had full access to all data in the study and provided final approval to submit the manuscript for publication.
Where can readers find more information on this clinical study?

The full title of the original publication in the *New England Journal of Medicine* is:

Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer.

You can read the abstract of the original publication at:


You can read more about the DESTINY-Breast01 study on the following websites:

- Enter the study number NCT03248492 into the search field at www.clinicaltrials.gov
- Enter the EudraCT identifier 2019-001512-34 in the search field at www.clinicaltrialsregister.eu

If you were a study participant and have questions about the results of this study, please speak with the doctor or staff at your study center.

Educational resources

- Read more about metastatic HER2-positive breast cancer on the Cancer.Net website at:
  https://www.cancer.net/cancer-types/breast-cancer-metastatic/types-treatment
- Learn about the National Comprehensive Cancer Network (or NCCN) clinical practice guidelines for treatment of breast cancer. These guidelines assist physicians in determining the best treatment for their patients. Read these guidelines at: https://www2.tri-kobe.org/nccn/guideline/breast/english/breast.pdf
- Read the NCCN patient guidelines for the treatment of metastatic breast cancer at:
  https://www.nccn.org/patients/guidelines/content/PDF/stage_iv_breast-patient.pdf

Additional resources for breast cancer patients:

- American Cancer Society: www.cancer.org
- Living Beyond Breast Cancer: www.ibbc.org
- Metavivor: www.metavivor.org
- Share Cancer Support: www.sharecancersupport.org
- Susan G. Komen: www.komen.org

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